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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HAYES, ROBERT CLINTON	
ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/594,192	GRONBORG ET AL.	
	Examiner	Art Unit	
	Robert C. Hayes, Ph.D.	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *65-72,89-94,98-109 and 113-128* is/are pending in the application.

4a) Of the above claim(s) *65-72,89-91,107-109 and 113-127* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *92-94,98-106 and 128* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *65-72,89-94,98-109 and 113-128* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/11/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group XVIII (claims 92-94, 98-106 & 128) in the reply filed on 4/30/09 is acknowledged. The traversal is on the ground(s) that the restriction between Groups XVIII and XIX is improper, and that Rule 13 does allow for multiple products and methods within a single application as long as those products and methods within a single application share the same or corresponding special technical features. This is not found persuasive because the previous Office action made clear that no "special" technical feature exists because no contribution over the prior art exists. See PCT search report Applicant filed with this application. Moreover, Group XIX is directed to gene therapy methods, versus administration of polypeptides (Group XVIII), and is further directed against treating immunological versus neurological disorders. Thus, Applicants' arguments are not persuasive. The requirement is still deemed proper and is therefore made FINAL.

Claims 65-72, 89-91, 107-109 and 113-127 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 4/30/09.

This application contains claim 65-72, 89-91, 107-109 and 113-127 drawn to an invention nonelected with traverse in the reply filed on 4/30/09. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Objections

2. Claims 92-94, 98-106 & 128 are objected to because base claim 89 recites improper Markush language. Elements within a Markush group are required to possess some structural similarity (e.g., be classified within the same class). See M.P.E.P. 2173.05(h). In addition, base claim 89 now recites nonelected inventions. Appropriate correction is required.

Claim Rejections - 35 USC § 101

3. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 105 is rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible asserted utility or a well established utility.

While the specification asserts a specific and substantial utility for the instant invention (e.g., pages 2-3 of the specification), "*preventing* apoptosis" (i.e., neuronal cell death) is not credible, because even normal aging results in death of neurons. Therefore, given the broadest reasonable interpretation consistent with that disclosed within the specification for the recitation of "*preventing* apoptosis", which requires no naturally occurring loss of even a single neuron, is not credible, by definition; especially as it relates to treating neurodegenerative disease states that are characterized by neuronal cell death that further have no known treatment. See MPEP 2107.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 92-94, 98-106 & 128 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The sole written description provided within the instant specification is using the full length human NsG33 polypeptide of SEQ ID NO: 3, rat polypeptide of SEQ ID NO: 13, or the mouse NsG33 polypeptide of SEQ ID NO: 8, and processed fragments thereof. However, one skilled in the art cannot reasonably visualize or predict what critical amino acid residues would structurally characterize the genus of polypeptides as encompassed by claim 92, 105, 106 & 128 (i.e., as it relates to "at least 80% identity", and C- or N-terminal fragments thereof). No other polypeptides with any functionally definable characteristics are described. No other species of NsG33 polypeptides are described. Nor has a single allelic variant of the human, mouse or rat encoded polypeptide sequence been described. Nor are any definable "*biologically active fragments* "of at least 50 contiguous amino acids" described. The specification fails to describe a single critical amino acid residue required for any definable function in the claimed genus. To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any

combination thereof. Therefore, in the absence of sufficient recitation of distinguishing identifying characteristics, because one skilled in the art cannot structurally visualized any other NsG33 amino acid sequences because none are described, and because even the three described different species of NsG33 do not reasonably demonstrate possession of a genus of "at least 80% identity" to any sequence because these sequences are more than "at least 80% identical", the written description requirement under 35 U.S.C. 112, first paragraph is not met. See MPEP 2163.

Accordingly, *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, *as of the filing date sought*, he or she was in possession *of the claimed invention*". "The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed* [emphasis added]".

5. Claims 92-94, 98-106 & 128 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a definable population of neurons with a structurally and functionally definable NsG33 polypeptide, does not reasonably provide enablement for generically treating any or all neurodegenerative disease states, or "preventing apoptosis", with structurally and functionally undefined NsG33 polypeptides, or putative biologically functional equivalents thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

First, the name, "NsG33 polypeptide", or variant or "biologically active fragment" thereof (e.g., as defined on pages 18-26 of the specification; as it relates to the recited %

identities, and fragments thereof) encompasses random insertions, deletions, or substitutions of amino acids, or any biologically functional equivalent polypeptide, which provides little or no structural characterization and no functional characteristics for knowing how to make and use the components required in the instantly claimed method. The specification fails to define what specific amino acids are critical for any NsG33-related function, or what specific amino acid residues distinguish the NsG33 polypeptides required in the currently claimed method from any different NsG33-related protein. In contrast, the skilled artisan would reasonably expect that random mutations to the protein of SEQ ID NO: 3, 8 or 13, etc would result using an inactive NsG33-related protein. For example, Rudinger states on page 3 that "it is impossible to attach a unique significance to any residue in a sequence. A given amino acid will not by any means have the same significance in different peptide sequences, or even in different positions of the same sequence". Rudinger then states on page 6 that "the significance of particular amino acid sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study". Therefore, the lack of guidance provided in the specification as to what minimal structural requirements are necessary for a NsG33-related protein's function would prevent the skilled artisan from determining whether any random modification or mutation to the NsG33 polypeptide of SEQ ID NOs: 3, 8, 13, etc could be made which retains the desired function of the instant invention, because any such random modification/ mutation/ truncation manifested within a structurally undefined polypeptide would be predicted to adversely affect the three-dimensional conformation of the polypeptide and therefore, result in a method that doesn't work, without requiring undue experimentation to determine otherwise.

Second, Figure 12 shows increased survival of rat striatal cultures treated with conditioned medium from transfected cells. Example 15 on pages 96-98 of the specification show that conditioned medium results in a 16% and 13% increase in the number of rat striatal neurons observed. However, no actual administration of any NsG33 polypeptide, or fragment thereof, is disclosed. Examples 8-12 then invite others to experiment to see if other neuronal populations may be responsive to NsG33. No specific populations of neurons that contain receptors responsive to NsG33 are disclosed, except for possibly rat striatal neurons. No reasonable guidance on how to successfully treat the neurodegenerative diseases recited in the claims is provided within the instant specification. Nor is any guidance provided within the specification, or known in the art, wherein a single recited disease state (i.e., as recited in the laundry list of diseases claimed to be treatable) is caused by dysfunction of the NsG33 gene. Finally, no disclosure exists within the instant specification on what actually constitutes a "therapeutically effective amount" for treating any given neurodegenerative disease state; or what parameters are to be assayed.

Third, the state of the art is such that numerous problems exist concerning effective *in vivo* regeneration/treatment of neurons, or generalized treatment of neuropathies, etc., because neuronal cell damage often results in cell death, and because "administration" of neurotrophic/growth factors to treat neurons requires solutions to not only bypassing the blood-brain barrier when treating CNS disorders but to selectively target responsive cells, if known, with enough neurotrophic/growth factor to elicit any response (i.e., through specific receptor binding). In other words, "effective" *in vivo* administration, as it relates to treating any neuronal cell type/disease state with any protein, requires that one skilled in the art must know how, when

or where the proposed invention is to be administered. In contrast, the instant specification has failed to disclose how these parameters are to be determined, except for enhancing the survival of rat striatal neurons.

The minimal requirement for successful treatment of a neurodegenerative disease is that *de novo* axonal cell growth be completed for a sufficient distance to re-establish a proximity relationship to the prior target. Importantly, effective treatment requires functional regeneration (i.e., synaptogenesis). However, regeneration does not occur either because processes fail to grow the necessary distance, they are in competition with other nearby neuronal processes not derived from the affected nerve, astrocytic scarring blocks axonal elongation, or because of misdirected axonal growth (e.g., see Jackowski, pgs. 309-310). In other words, neurons do not regenerate in the CNS (e.g., Jackowski, pg. 305, last *pp*). In contrast, the instant specification fails to provide any guidance on how to prevent any damaged neuron from degenerating, or how to prevent any neuron from dying that is damaged, or how any neurodegenerative pathological condition, each with their unique etiology, can be effectively treated with any NsG33 polypeptide; nor how to assay such *in vivo*.

In conclusion, because no universal treatment is known or accepted in the art for treating all neurodegenerative disease states, because the critical amino acid residues within NsG33 required for any definable functional activity is unknown and not disclosed, because one of ordinary skill in the at would not reasonably be able to successfully predict whether any "symptom" can be treated through administration of any NsG33-related polypeptide because none are specifically recited, because it is unknown and not disclosed when the skilled artisan has successfully practiced the claimed invention because not a single cell that possesses a NsG33

receptor is known in the art or disclosed to be specifically associated with a specific disease state, because not a single neurodegenerative disease state is disclosed that shows some efficacy to treatment with a NsG33 polypeptide, and because it is unknown how to "treat' disease states with no known causes and wherein the neurodegenerative disease state is characterized by death of specific populations of neurons, one of ordinary skill in the art would not reasonably know how to make and use the invention without requiring undue experimentation to discover such after-the-fact.

6. Claims 93, 94, 100, 102 & 103 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is confusing how undefined "associated symptoms" relate to treating anything, especially when a symptom is not a "disease, disorder, or damage…" within itself.

Claim 93 further is dependent on non-elected base claim 89, which has been withidrawn, and therefore, is incomplete.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 92-94, 98-106 & 128 are rejected under 35 U.S.C. 102(b) as being anticipated by Innogenetics N.V. (WO 01/39786; IDS Ref # B2).

Innogenetics teach the human SMAF-2 polypeptide of SEQ ID NO: 4, which is 100% identical to SEQ ID NO: 3 of the instant invention (e.g. pg. 6 & Figure 1), and treatment of patients with multiple sclerosis (e.g., pgs 6 & 11); thereby, anticipating all claims because patients with MS are patients with a pathological condition associated with the nervous system (i.e., both CNS and PNS), in which numerous neuronal systems are affected, as currently broadly claimed. It is noted that the sole method step recited in the claims is "administering" and "exposing said neuronal cell", which Innogenetics clearly teach.

8. Claims 92-94, 98-106 & 128 are rejected under 35 U.S.C. 102(b) as being anticipated by Tang et al/ HYSEQ, INC (WO 01/57190; IDS Ref # B6).

Tang et al teach administering the polypeptide of SEQ ID NO: 1401, which is 100% identical to SEQ ID NO: 3 of the instant invention (e.g., see pgs 4-5, 29 & 65-66), to treat pathological nervous system disorders, which include "lesions of either the central (including spinal cord, brain) or peripheral nervous systems", and in particular include traumatic brain injury, ischemic lesions/stroke, infectious lesions, Parkinson's Disease, Alzheimer's Disease, amyotrophic lateral sclerosis, diabetic neuropathy, neurological lesions associated with metabolic and vitamin B12/folic acid deficiency, alcoholism or toxic injury, multiple sclerosis, etc. (e.g., pgs. 59-60; as it relates to claims 92-94 & 98-104). In that administration of Tang's polypeptide inherently affects apoptosis, and enhances survival of the associated affected neuron populations after administration and exposing the neurons of the CNS and PNS to Tang's

polypeptide, the limitations of claims 105, 106 and 128 are further anticipated. It is noted that the sole method step recited in the claims is "administering" and "exposing said neuronal cell", which Tang et al. clearly teach.

Conclusion

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (571) 272-0885. The examiner can normally be reached on Monday through Thursday from 9:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached on (571) 272-0911. The fax phone number for this Group is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Robert C. Hayes, Ph.D./
Primary Examiner, Art Unit 1649
June 15, 2009